L27 ANSWER 1 OF 1 USPATFULL
ACCESSION NUMBER: 97:66114 USPATFULL
TITLE: Inhibition of the degradation of connective tissue matrix protein components in mammals
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PATENT INFORMATION:	US 5652227	19970729	
APPLICATION INFO.:	US 1995-380581	19950130	(8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Seidleck, James J.
ASSISTANT EXAMINER: Cooney, Jr., John M.
LEGAL REPRESENTATIVE: Browdy and Neimark
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 730
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L27 ANSWER 1 OF 1 USPATFULL
CLM What is claimed is:
1. A method of reducing of reducing a pathological excess of mammalian collagenolytic **enzyme** activity and an excessive **degradation** of connective tissue **matrix** protein components in a mammal in need thereof comprising: administering to said mammal a bisphosphonate in an amount which is. . . . rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne**, psoriasis, loosening of end-osseal hip-protheses.

. . . rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne**, psoriasis, loosening of end-osseal hip-protheses.

. . . of wounds, burns, lesions, ulcers, rheumatoid arthritis or other arthritides, cysts, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne** and psoriasis.

1. A method of reducing of reducing a pathological excess of mammalian collagenolytic **enzyme** activity and an excessive **degradation** of connective tissue **matrix** protein components in a mammal in need thereof comprising: administering to said mammal a bisphosphonate in an amount which is effective in reducing the matrix metalloproteinase (NMP) activity in said mammal.

2. The method of claim 1, which comprises administering to said mammal an effective amount of bisphosphonate which results in a significant reduction of the MMP dependent protein degradation in said mammal.

3. The method of claim 1, wherein said bisphosphonates comprises a bisphosphonate which is active as an inhibitor against at least one matrix metalloproteinase (MMP).

4. The method of claim 3, wherein said matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8 and a combination of MMP-1 and MMP-8, and wherein said mammal is a human having an increased level of MMP-1, MMP-8 or both MMP-1 and MMP-8.

5. The method of claim 1, wherein said bisphosponate is a geminal bisphosphonate having the general formula ##STR2## wherein R' and R" independently stand for a hydrogen or a halogen atom, a hydroxy, optionally substituted amino or optionally substituted thio group or an optionally substituted hydrocarbon residue.

6. The method of claim 5, wherein said bisphosphonate is selected from the group consisting of (1-hydroxyethylidene)bis-phosphonate, (dichloromethylene)bis-phosphonate (clodronate), (3-amino-1-hydroxypropylidene)bisphosphonate, (4-amino-1-hydroxybutylidene)bis-phosphonate, {[4-chlorophenyl)thio]methylene}bis-phosphonate, (6-amino-1-hydroxyhexylidene)bis-phosphonate, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-phosphonate, [3-(dimethylamino)-1-hydroxypropylidene]bis-phosphonate, [1-hydroxy-3-(methylpentylamino)propylidene]bis-phosphonate or a mixture thereof.

7. The method of claim 6, wherein said bisphosphonate is clodronate.

8. The method of claim 1, wherein said bisphosphonate is administered in

a way selected from the group consisting of oral, intravenous, parenteral, subcutaneous and topical administration.

9. The method of claim 1 wherein said mammal is a human selected from a populace susceptible to an excess degradation of connective tissue matrix protein components selected from the group consisting of diabetics and health care workers, and wherein said bis-phosphonate is administered prophylactically.

10. The method of claim 1 wherein said mammal is a human, with the proviso that such human is not (a) a patient in need of a skeletal marker in the form of .sup.99m technetium derivatives for diagnostic purposes in nuclear medicine, (b) a patient in need of administration of

an anti-osteolytic agent, (c) a patient with ectopic calcification and ossification in need of an inhibitor of calcification, or (d) a patient in need of an anti-tartar agent.

11. The method according to claim 10 wherein said human is a patient selected from the group of patients in need of treatment of wounds, burns, fractures, lesions, ulcers, cancer and metastasis progression in connective tissues, rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne**, psoriasis, loosening of end-osseal hip-protheses.

12. The method according to claim 1, wherein said excessive degradation

of connective tissue matrix protein components in mammals comprises a physiological or pathological condition selected from the group consisting of wounds, burns, fractures, lesions, ulcers, cancer and metastasis progression in connective tissues, rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne**, psoriasis, loosening of end-osseal hip-protheses.

13. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises periodontitis.

14. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises peri-implantitis.

15. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises cancer and metastasis progression in connective tissues.

16. A method of inhibiting extracellular activity of MMP-1, MMP-8 or both MMP-1 and MMP-8, in a mammal in need thereof comprising: administering to said mammal a bisphosphonate in an amount which is effective in reducing the extracellular matrix MMP-1, MMP-8 or both MMP-1 and MMP-8 activity in said mammal.

17. A method according to claim 16 wherein said mammal is a human patient having an increased level of MMP-1, MMP-8 or both MMP-1 and MMP-8 and is in need of a treatment selected from the group consisting of treatments of wounds, burns, lesions, ulcers, rheumatoid arthritis or other arthritides, cysts, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne** and psoriasis.

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L28 ANSWER 23 OF 54 USPATFULL

SUMM . . . methods of treating the hyperandrogenic conditions of androgenic alopecia including male pattern baldness, acne vulgaris, seborrhea, and female hirsutism by **oral**, systemic, parenteral or **topical** administration of the novel compounds of Formula I either alone or in **combination** with a 5.alpha.-reductase 2 inhibitor, and/or further in **combination** with: a potassium channel opener, e.g., minoxidil; an antiandrogen, e.g., flutamide; a retinoid, e.g., tretinoin or isotretinoin; an alpha-1 receptor. . .

SUMM . . . the prevention and/or treatment of prostatic cancer, the compounds of the instant invention can be used alone or can be **combined** with a therapeutically effective amount of a 5.alpha.-reductase 2 inhibitor, such as finasteride, in a single **oral**, systemic, or parenteral pharmaceutical dosage formulation. Also, for the skin and scalp related disorders of acne vulgaris, androgenic alopecia including. . . baldness, seborrhea, and female hirsutism, the compounds of the instant invention and a 5.alpha.-reductase 2 inhibitor can be formulated for **topical** administration. Alternatively, a **combined** therapy can be employed wherein the compound of Formula I and the 5.alpha.-reductase 2 inhibitor are administered in separate **oral**, systemic, parenteral or **topical** dosage formulations. For example, a compound of Formula I and e.g., finasteride can be administered in a single **oral** or **topical** dosage formulation, or each active agent can be administered in a separate dosage formulation, e.g., in separate **oral** dosage formulations, or an **oral** dosage formulation of finasteride in **combination** with a **topical** dosage formulation of a compound of Formula I. See, e.g., U.S. Pat. Nos. 4,377,584 and 4,760,071 which describe dosages and. . .

SUMM Furthermore, administration of a compound of the present invention in **combination** with a therapeutically effective amount of a potassium channel opener, such as minoxidil, cromakalin, pinacidil, a compound selected from the. . . used for the treatment of androgenic alopecia including male pattern baldness. The active agents can be administered in a single **topical** dosage formulation, or each active agent can be administered in a separate dosage formulation, e.g., in separate **topical** dosage formulations, or an **oral** dosage formulation of a compound of Formula I in **combination** with a **topical** dosage formulation of, e.g., minoxidil. See, e.g., U.S. Pat. Nos. 4,596,812, 4,139,619 and WO 92/02225, published 20 Feb. 1992, for. . .

CLM What is claimed is:

6. A method for treating the condition of **acne** vulgaris comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a. . .

8. A method for treating the conditioning of **acne** vulgaris comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a. . .

ACCESSION NUMBER: 1998:39528 USPATFULL

TITLE: 16-substituted-4-aza-3-oxo-androstane as 5-alpha-reductase isozyme 1 inhibitors

INVENTOR(S): Durette, Philippe L., New Providence, NJ, United States

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Sahoo, Soumya P., Old Bridge, NJ, United States
Rasmusson, Gary H., Watchung, NJ, United States
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PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5739137	19980414	
	WO 9511254	19950427	
APPLICATION INFO.:	US 1996-601042	19960228	(8)
	WO 1994-US12071	19941021	
		19960228	PCT 371 date
		19960228	PCT 102(e) date

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-141153, filed on 21 Oct 1993, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Daus, Donald G.

L28 ANSWER 24 OF 54 USPATFULL

SUMM . . . methods of treating the hyperandrogenic conditions of androgenic alopecia including male pattern baldness, acne vulgaris, seborrhea, and female hirsutism by **oral**, systemic, parenteral or **topical** administration of the novel compounds of Formula I either alone or in **combination** with a 5.alpha.-reductase 2 inhibitor, and/or further in **combination** with: a potassium channel opener, e.g., minoxidil; an anti-androgen, e.g., flutamide; a retinoid, e.g., tretinoin or isotretinoin; an alpha-1 receptor. . .

SUMM . . . prostatitis and the treatment of prostatic cancer, the compounds of the instant invention can be used alone or can be **combined** with a therapeutically effective amount of a 5.alpha.-reductase 2 inhibitor, such as finasteride, in a single **oral**, systemic, or parenteral pharmaceutical dosage formulation. Also, for the skin and scalp related disorders of acne vulgaris, androgenic alopecia including. . . baldness, seborrhea, and female hirsutism, the compounds of the instant invention and a 5.alpha.-reductase 2 inhibitor can be formulated for **topical** administration. Alternatively, a **combined** therapy can be employed wherein the compound of Formula I and the 5.alpha.-reductase 2 inhibitor are administered in separate **oral**, systemic, parenteral or **topical** dosage formulations. For example, a compound of Formula I and e.g., finasteride can be administered in a single **oral** or **topical** dosage formulation, or each active agent can be administered in a separate dosage formulation, e.g., in separate **oral** dosage formulations, or an **oral** dosage formulation of finasteride in **combination** with a **topical** dosage formulation of a compound of Formula I. See, e.g., U.S. Pat. Nos. 4,377,584 and 4,760,071 which describe dosages and. . .

SUMM Furthermore, administration of a compound of the present invention in **combination** with a therapeutically effective amount of a potassium channel opener, such as minoxidil, cromakalin, pinacidil, a compound selected from the. . . used for the treatment of androgenic alopecia including male pattern baldness. The active agents can be administered in a single **topical** dosage formulation, or each active agent can be administered in a separate dosage formulation, e.g., in separate **topical** dosage formulations, or an **oral** dosage formulation of a compound of Formula I in **combination** with a **topical** dosage formulation of, e.g., minoxidil. See, e.g., U.S. Pat. Nos. 4,596,812, 4,139,619 and WO 92/02225, published 20 Feb. 1992, for. . .

CLM What is claimed is:

7. A method for treating the condition of **acne** vulgaris consisting essentially of administering to a mammal in need of such treatment a therapeutically effective amount of a compound. . .

8. A method for treating the condition of **acne** vulgaris consisting essentially of administering to a mammal in need of such treatment a therapeutically effective amount of a compound. . .

14. A method for treating the condition of **acne** vulgaris consisting essentially of administering to a mammal in need of such treatment a therapeutically effective amount of a compound. . .

22. A method for treating the condition of **acne** vulgaris consisting essentially of administering to a mammal in need of such treatment a therapeutically effective amount of a compound. . .

ACCESSION NUMBER: 1998:17321 USPATFULL

TITLE:	16-substituted-4-aza-androstane 5-alpha-reductase isozyme 1 inhibitors
INVENTOR(S):	Durette, Philippe L., New Providence, NJ, United States Hagmann, William K., Westfield, NJ, United States Lanza, Jr., Thomas J., Edison, NJ, United States Sahoo, Soumya P., Old Bridge, NJ, United States Rasmusson, Gary H., Watchung, NJ, United States Tolman, Richard L., Warren, NJ, United States von Langen, Derek, Fanwood, NJ, United States
PATENT ASSIGNEE(S):	Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5719158	19980217
APPLICATION INFO.:	US 1995-463544	19950605 (8)

RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1993-141153, filed on 21 Oct 1993, now abandoned
DOCUMENT TYPE:	Utility
PRIMARY EXAMINER:	Daus, Donald G.
LEGAL REPRESENTATIVE:	Fitch, Catherine D.; Winokur, Melvin
NUMBER OF CLAIMS:	23
EXEMPLARY CLAIM:	1

L6 ANSWER 3 OF 4 USPATFULL

SUMM . . . as seen in periodontium (Sorsa et al., Infect. Immun. 1992, 60:
4491-4495). Recent studies indicate that a serine protease, i.e., **elastase**, may play a role in connective tissue breakdown and tissue invasion in the Dunning rat model of cancer invasion and. . .

SUMM . . . cartilage degradation (Greenwald et al., Bone 1998, 22:33-38; Ryan et al., Curr. Op. Rheumatol. 1996, 8;238-247). MMP-20 is expressed by **oral** squamous cell carcinoma cells (Salo et al., J. Dent. Res. 1998, 77:829, Abstr. No. 1978). Bourguignon et al. (Mol. Biol.. .
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SUMM . . . deficiency syndrome (AIDS), burns, wounds such as bed sores and
varicose ulcers, fractures, trauma, gastric ulceration, skin diseases such as **acne** and psoriasis, lichenoid lesions, epidermolysis bullosa, aphthae (reactive **oral** ulcer), dental diseases such as periodontal diseases, peri-implantitis, jaw cysts and other periapical cysts, dental conditions which are the target of root canal treatment or endodontic treatment, related diseases, **external** and intrinsic root resorption, caries etc.

SUMM The serine proteinases include human leukocyte **elastase** (HLE) and cathepsin G, and additional serine proteinases are involved in the cascade of pathways involved in connective tissue breakdown. . .

SUMM MMP's and serine proteinases can work in **combinations** to bring about destruction of most of the elements of the extracellular matrix and basement membranes. As examples of the. . . between MMP's and serine proteinases during tissue breakdown, 1) cathepsin G can activate MMP-8; 2) the serine proteinase Human Leukocyte **Elastase** (HLE) can inactivate TIMP's, the major endogenous Tissue Inhibitors of Matrix Metalloproteinases, 3) MMP-8 and MMP-9 can activate .alpha..sub.1 -Proteinase Inhibitor (.alpha..sub.1 -PI), the major endogenous inhibitor of human leukocyte **elastase**, (S. K. Mallya, et al., Annuals of the New York Academy of Science, 1994, 732:303-314) and 4) tumor-associated-trypsin-2 can efficiently. . .

SUMM U.S. Pat. No. 5,773,430 to Simon et al. describes using hydrophobic tetracyclines to inhibit excess leukocyte **elastase** serine proteinase activity in a biological system.

DETD . . . marked inflammation in the periodontal tissues and induces elevated levels of tissue-destructive matrix metalloproteinases (MMPs) and serine proteinases such as **elastase** in the gingiva leading to severe alveolar bone resorption and bone loss around the affected teeth, all within the 7-day. . . of these destructive pathways, often
reducing these levels in the endotoxin-injected tissues to the normal levels of collagenases, gelatinases and **elastase** seen in the saline-injected (control) tissues.

DETD . . . synergistically inhibits the activities of pure human cell bound MT.sub.1 -MMP and extracellular collagenases, gelatinases (extracellular MMP's) as well as **elastase** (serine proteinase).

DETD . . . on day 7. As described above, the gingival tissues were dissected, extracted and the partially-purified extracts analyzed for neutral proteinase (**elastase** and matrix metalloproteinase) activities, and both tooth mobility and alveolar bone loss were assessed.

DETD **elastase** activity was measured spectrophotometrically using a synthetic peptide substrate specific for neutrophil (inflammatory cell) **elastase**.

DETD . . . 1997, 36:310-317). It is noteworthy that all of these assays